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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/486,971	05/19/2000	VELI-MATTI LEHTOLA	933-154PCT	7050

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EXAMINER	
BENNETT, RACHEL M	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 01/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/486,971	LEHTOLA ET AL.	
	Examiner	Art Unit	
	Rachel M. Bennett	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6,11 and 14-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-4, 6, 11, 14-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114 was filed in this application after a decision by the Board of Patent Appeals and Interferences, but before the filing of a Notice of Appeal to the Court of Appeals for the Federal Circuit or the commencement of a civil action. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 12/1/03 has been entered.

Specification

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. Claims 1, 3-4, 6, 11, 14-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Posti et al. (US 5525354) in further view of Sherwood (WO 96/21429) and Remington's Pharmaceutical Sciences.

Posti discloses a pharmaceutical preparation for oral use containing a pharmacologically acceptable salt of a dichloromethylene bisphosphonic acid, a clodronate, especially disodium clodronate (see abstract, column 1 lines 6-10). The preparation may also contain additives, such as carriers, diluents, fillers, lubricants, and disintegrating agents, which are all known in the art (see column 2 lines 18-22). More specifically, microcrystalline cellulose as a filler and colloidal silicon dioxide may be used as a lubricant (see column 2 lines 41-51). The preparation is carried out using known tabletting, granulating or pelletization techniques (see column 2 lines 52-54). Example 1 illustrates a tablet comprising disodium clodronate, microcrystalline cellulose and silicon dioxide. The desired amount of clodronate can vary within wide limits from 10 to 95% by weight (see column 2 lines 22-25). The preparation also comprises of microcrystalline cellulose and silicon dioxide comprises about 8 to 20% by weight, and lubricants and/or disintegrants comprise about 0.5 to 10% by weight (see example 1). Posti does not disclose preparing the microcrystalline cellulose and silicon dioxide in a particulate agglomerate of co-processed microcrystalline cellulose and silicon dioxide.

Sherwood discloses a microcrystalline cellulose-based excipient having improved compressibility, whether utilized in direct compression, dry granulation, or wet granulation formulations. The excipient is an agglomerate of microcrystalline cellulose particles and from about 0.1% to about 20% silicon dioxide particles, by weight of the microcrystalline silicon dioxide particles, by weight of the microcrystalline cellulose, wherein the microcrystalline

cellulose and silicon dioxide are in intimate association with each other (see abstract). Sherwood discloses known methods of tableting. Lubricants are typically added to avoid the material(s) being tabletted from sticking. In addition to lubricants, solid dosage forms often contain diluents. Diluents are frequently added in order to increase the bulk weight of the material to be tabletted in order to make the tablet a practical size for compression. Disintegrants are often included in order to ensure the ultimately prepared compressed solid dosage form has an acceptable disintegrating rate in an environment of use. Typically excipients are added to the formulation, which impart good flow and compression characteristics to the material as a whole. Compared to other directly compressible excipients, microcrystalline cellulose is generally considered to exhibit superior compressibility and disintegration properties (see pages 2 and 4). Sherwood's excipient comprises a particulate agglomerate of copressed microcrystalline cellulose and form about 0.1% to about 20% silicon dioxide, by weight of the microcrystalline cellulose, the microcrystalline cellulose and silicon dioxide being in intimate association with each other (see page 9). Advantages of the disclosed excipient include excellent disintegration properties and improved compressibility (see page 11). By "intimate association", it is meant that the silicon dioxide has in some manner been integrated with the microcrystalline cellulose particles e.g., via a partial coating of the microcrystalline cellulose particles, as opposed to a chemical interaction of the two ingredients. It is most preferred the microcrystalline cellulose and silicon dioxide are coprocessed, resulting in an intimate association of these ingredients, rather than being combined as a dry mixture. After a uniform mixture of the ingredients is obtained in a suspension, the suspension is dried to provide a plurality of microcrystalline cellulose-based excipient particles

having enhanced compressibility. It is preferred that the suspension be dried using spray-drying techniques, as they are known in the art (see page 21).

Remington discloses microcrystalline cellulose as a tablet diluent and disintegrant and silicon dioxide as a tablet diluent and as a suspending and thickening agent in pharmaceutical preparations (see pages 1319 and 1325).

It is the position of the examiner, that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the composition of Posti by substituting silicified microcrystalline cellulose taught by Sherwood for the microcrystalline cellulose and silicon dioxide of Posti because of the expectation of achieving excellent disintegration properties and improved compressibility as taught by Sherwood. Remington discloses microcrystalline cellulose and silicon dioxide are known in the art as excipients for tableting, while Sherwood discloses the combination of the two has improved characteristics. Therefore, substituting one excipient, as taught by Sherwood, for two excipients as taught by Posti, would not only have the advantages taught by Sherwood, but would also add convenience to the overall process of making. The expected result would a tablet comprising dicholoromethylene biphosphonic acid and silicified microcrystalline cellulose as the excipient.

Response to Arguments

5. Applicant's arguments filed 12/1/03 have been fully considered but they are not persuasive.

Applicants argue the essential feature of the Posti reference is the enteric coating. However, the examiner refers to Posti '354, Example 1, wherein Posti discloses a prepared tablet

in the first stage and then later the prepared tablet was coated with a coating solution. Furthermore, Post discloses an uncoated tablet in col. 4, in both the methods and results section. Lastly, in the decision by the Board, dated 9/30/03, page 7, the Board states "...the presence or absence of an enteric coating fails to distinguish the claimed subject matter from the disclosure of the references on record."

The primary reference, Posti '354, teaches the active ingredient, the specific amounts, and the excipients microcrystalline cellulose and silicone dioxide. The method of manufacturing is disclosed in Example 1 of Posti' 354. The secondary references, Sherwood (WO 96/21429) and Remington's Pharmaceutical Science, are added to show the excipient, silicified microcrystalline cellulose (SMCC-which is microcyrstalline cellulose and silicon dioxide in an intimate association with each other) may be substituted for the microcyrstalline cellulose and silicone dioxide. The motivation for such a substitution is found in the secondary references, specifically Sherwood wherein Sherwood's excipient comprises a particulate agglomerate of copressed microcrystalline cellulose and form about 0.1% to about 20% silicon dioxide, by weight of the microcrystalline cellulose, the microcrystalline cellulose and silicon dioxide being in intimate association with each other (see page 9). Advantages of the disclosed excipient include excellent disintegration properties and improved compressibility (see page 11). By "intimate association", it is meant that the silicon dioxide has in some manner been integrated with the microcrystalline cellulose particles e.g., via a partial coating of the microcrystalline cellulose particles, as opposed to a chemical interaction of the two ingredients. Therefore, the rejection has been maintained because there is reasonable motivation for one of ordinary skill in the art to substitute the excipient taught by Sherwood for the excipients taught by Posti because

Remington discloses microcrystalline cellulose and silicon dioxide are known in the art as excipients for tableting, while Sherwood discloses the combination of the two has improved characteristics such as excellent disintegration properties and improved compressibility. Therefore, substituting one excipient, as taught by Sherwood, for two excipients as taught by Posti, would not only have the advantages taught by Sherwood, but would also add convenience to the overall process of making.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rachel M. Bennett whose telephone number is (703) 308-8779 (as of 2/4/04, (571) 272-0589). The examiner can normally be reached on Monday through Friday, 8:00 A.M. to 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on (703) 308-2927 (as of 2/4/04, (571) 272-0602). The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

rmb

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
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